Full Text AR-94-006

PILOT STUDY: INTRAVENOUS ANTIBIOTICS FOR RHEUMATOID ARTHRITIS

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PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) requests applications to initiate a pilot clinical study designed to test the hypothesis that intravenous antibiotic therapy is an effective and safe treatment for rheumatoid arthritis.
The budget appropriation report language for the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) indicated that funds were provided to "...initiate a pilot clinical trial to study the efficacy of intravenous antibiotic therapy in treating rheumatoid arthritis. This study should include measures of disease activity and, pending the outcome, be considered the initial step in developing a multicenter clinical trial."

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This RFA, Pilot Study: Intravenous Antibiotics for Rheumatoid Arthritis, is related to the priority area of chronic disabling conditions.

Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0) or "Healthy People 2000" (Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-783-3238).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Applications from minority individuals and women are encouraged.

MECHANISM OF SUPPORT

This RFA will use the National Institutes of Health (NIH) individual research project grant (R01). The application may include subcontracts or consortia with multiple institutions. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period for applications submitted in response to the present RFA may not exceed two years. The anticipated award date is September 1994.

Because the nature and scope of the research proposed in response to this RFA may vary, it is anticipated that the size of an award will vary also.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resources for conducting the proposed research. If so, a letter of agreement from either the GCRC program director or Principal Investigator should be included within the application.

This RFA is a one-time solicitation. Future unsolicited competing continuation applications will compete with all investigator-initiated applications and be reviewed according to the customary peer review procedures.

FUNDS AVAILABLE

A sum of $500,000 (total cost) is available for this RFA. One award is anticipated. Of this amount, $50,000 is reserved for the operation of a Data and Safety Monitoring Committee.

RESEARCH OBJECTIVES

Background

The role of infectious agents in the pathogenesis of rheumatoid arthritis is uncertain. In 1971, a small clinical trial of low dose tetracycline treatment for rheumatoid arthritis demonstrated no beneficial effect (Skinner et al., Arthritis Rheum 1971; 14:727-35). However, the discovery that tetracyclines inhibit collagenase, thus potentially protecting against joint destruction in inflammatory arthritis, has recently led investigators to reconsider antibiotic therapy for this disease. In two small open trials oral minocycline appeared to improve outcome in rheumatoid patients (Breedveld et al., J Rheumatol 1990; 17:43-6; Langevitz et al., J Rheumatol 1992; 19:1502-4). In April, 1991, the NIAMS initiated a double-blind, placebo-controlled clinical trial of oral minocycline. The results of this trial, as well as the results of a similar trial in the Netherlands, were presented at the 57th Annual Meeting of the American College of Rheumatology in San Antonio, Texas, on November 8, 1993 (Tilley et al., Arthritis Rheum 1993;36:s46 and Kloppenburg et al., Arthritis Rheum 1993;36:s47). The American study showed modest benefit and low toxicity, while the European study showed little benefit and moderate toxicity. The NIAMS-sponsored trial compared 200 mg of minocycline per day with placebo in 219 patients in a 48 week, randomized double blind trial. Patients included in this study met the established criteria for RA and remained on non-steroidal antiinflammatory drugs or low dose prednisone. Changes of 50 per cent or more improvement occurred in 53 percent of minocycline treated patients and in 36 percent of placebo patients. Dizziness and nausea were reported by patients in both groups. The study from the Netherlands compared 200 mg minocycline daily with placebo in 80 patients with RA. Few clinically meaningful changes were observed; statistically significant improvement in the numbers of painful joints were reported. Full publications of both of these studies are pending.

In a further effort to provide a basis for the use of antibiotics in the therapy of RA, the NIAMS launched a RFA in 1993 to study the role of infectious agents in the pathogenesis of rheumatic diseases. Awards made for this RFA included applications directly addressing the involvement of mycoplasmas and other agents in the onset of RA; however, no clinical trials were proposed by the applicants.

For many years the Senate Appropriations Committee has expressed an interest in the infectious theory of rheumatoid arthritis, especially the possibility that mycoplasma organisms cause rheumatoid arthritis. The NIAMS has responded by issuing the above RFA, a Program

Announcement (88-03, Research on Infectious Agents in the Etiology of Rheumatoid Arthritis, February 1988), and by submitting reports on this topic to the Committee in December 1982, December 1983, November 1984, and January 1993. In its 1994 Appropriations Report, the Committee directed "that NIAMS, within the funds provided, initiate a pilot clinical trial to study the efficacy of intravenous antibiotic therapy in treating rheumatoid arthritis. The study should include measures of disease activity... " The NIAMS now solicits applications to fulfill this directive.

Goals and Scope

The goal of this RFA, accordingly, is to encourage development of a pilot clinical research project designed to test the hypothesis that intravenous antibiotic therapy is a potentially effective and safe therapy for RA.

STUDY POPULATIONS

SPECIAL INSTRUCTIONS TO APPLICANTS REGARDING IMPLEMENTATION OF NIH POLICIES CONCERNING INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH STUDY POPULATIONS

NIH policy is that applicants for NIH clinical research grants and cooperative agreements are required to include minorities and women in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study; special emphasis must be placed on the need for inclusion of minorities and women in studies of diseases, disorders and conditions which disproportionately affect them. This policy is intended to apply to males and females of all ages. If women or minorities are excluded or inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale must be provided.

The composition of the proposed study population must be described in terms of gender and racial/ethnic group. In addition, gender and racial/ethnic issues must be addressed in developing a research design and sample size appropriate for the scientific objectives of the study. This information must be included in the form PHS 398 (rev. 9/91) in Sections 1-4 of the Research Plan AND summarized in Section 5, Human Subjects. Applicants are urged to assess carefully the feasibility of including the broadest possible representation of minority groups. However, NIH recognizes that it may not be feasible or appropriate in all research projects to include representation of the full array of United States racial/ethnic minority populations

(i.e., Native Americans [including American Indians or Alaskan Natives], Asian/Pacific Islanders, Blacks, Hispanics).

The rationale for studies on single minority population groups should be provided.

For the purpose of this policy, clinical research is defined as human biomedical and behavioral studies of etiology, epidemiology, prevention (and preventive strategies), diagnosis, or treatment of diseases, disorders or conditions, including, but not limited to, clinical trials.

The usual NIH policies concerning research on human subjects also apply. Basic research or clinical studies in which human tissues cannot be identified or linked to individuals are excluded. However, every effort should be made to include human tissues from women and racial/ethnic minorities when it is important to apply the results of the study broadly, and this should be addressed by applicants.

For foreign awards, the policy on inclusion of women applies fully; since the definition of minority differs in other countries, the applicant must discuss the relevance of research involving foreign population groups to the United States' populations, including minorities.

If the required information is not contained within the application, the application will be returned.

Peer reviewers will address specifically whether the research plan in the application conforms to these policies. If the representation of women or minorities in a study design is inadequate to answer the scientific question(s) addressed AND the justification for the selected study population is inadequate, it will be considered a scientific weakness or deficiency in the study design and reflected in assigning the priority score to the application.

All applications for clinical research submitted to NIH are required to address these policies. NIH funding components will not award grants or cooperative agreements that do not comply with these policies.

LETTER OF INTENT

Prospective applicants are asked to submit, by June 1, 1994, a letter of intent that includes a descriptive title of the proposed research, the name, address, and telephone number of the Principal Investigator, the identities of other key personnel and participating institutions, and the

title PILOT STUDY: INTRAVENOUS ANTIBIOTICS FOR RHEUMATOID ARTHRITIS and the RFA number: AR-94-006.

Although a letter of intent is not required, is not binding, and does not enter into the review of subsequent applications, the information that it contains allows NIAMS staff to estimate the potential review workload and to avoid conflict of interest in the review.

The letter of intent is to be sent to Dr. Susana A.S. Sztein at the address listed under INQUIRIES.

APPLICATION PROCEDURES

The applications should include detailed description and justification of the antibiotic regimens chosen. Special attention should be paid to describing how patients will be monitored for clinical activity and how patients will be monitored for toxicity, including opportunistic infections. Because patient safety is a paramount concern, an independent Data and Safety Monitoring Committee (DSMC) will be a required component of the study. The DSMC will be appointed by the applicant institution. Assessment of the adequacy of the DSMC will be an important review criterion as well as an award criterion. An independent Data and Safety Monitoring Board is a required component of the study and must include an NIAMS representative. Full instructions for the establishment of such a Board are available from Dr. Susana A. S. Sztein, at the address listed under INQUIRIES. The applications should also include a description of the potential advantages and disadvantages of the use of antibiotics in RA, the advantages of using intravenous over oral antibiotics, as well as the potential mechanisms underlying any observed therapeutic effects. Careful description of control groups must be included as well as copies of the informed consent forms. The Food and Drug Administration (FDA) requires that Investigational New Drug (IND) approval be obtained if a drug is to be used for a non-label purpose. It is the applicant's responsibility to obtain such approval.

The research grant application form PHS 398 (rev. 9/91) is to be used in applying for these grants. These forms are available at most institutional offices of sponsored research; from the Office of Grants Information, Division of Research Grants, National Institutes of Health, 5333 Westbard Avenue, Room 449, Bethesda, MD 20892, telephone 301/435-0714; and from the NIH program administrator listed under INQUIRIES.

The RFA label available in the PHS 398 (rev. 9/91) application form must be affixed to the bottom of the face page of the application. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the

RFA title and number must be typed on line 2a of the face page of the application form and the YES box must be marked.

Submit a signed, typewritten original of the application, including the Checklist, and three signed, photocopies, in one package to:

Division of Research Grants
National Institutes of Health
Westwood Building, Room 240
Bethesda, MD 20892**

At the time of submission, two additional copies of the application must also be sent to:

Dr. Tommy L. Broadwater
Review Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 406
Bethesda, MD 20892
Telephone: (301) 594-9979
FAX: (301) 594-9673

Applications must be received by July 13, 1994. If an application is received after that date, it will be returned to the applicant without review. The Division of Research Grants (DRG) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The DRG will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by DRG and responsiveness by the NIAMS. Incomplete applications will be returned to the applicant without further consideration. If the application is not responsive to the RFA, NIAMS staff will contact the applicant to determine whether to return the application to the applicant or submit it for review in competition with unsolicited applications at the next review cycle.

Applications may be triaged by a peer review group convened by NIAMS on the basis of relative competitiveness. The NIH will withdraw from further competition those applications judged to be non-competitive for award and notify the applicant Principal Investigator and institutional official. Those applications judged to be competitive will undergo further scientific merit review. Those applications that are complete and responsive will be evaluated in accordance with the criteria stated below for scientific/technical merit by an appropriate peer review group convened by the NIAMS. The second level of review will be provided by the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council.

Review criteria for RFAs are generally the same as those for unsolicited research grant applications.

o scientific, technical, or medical significance and originality of proposed research;

o appropriateness and adequacy of the experimental approach and methodology proposed to carry out the research;

o qualifications and research experience of the Principal Investigator and staff, particularly, but not exclusively, in the area of the proposed research;

o availability of the resources necessary to perform the research;

o appropriateness of the proposed budget and duration in relation to the proposed research; and

To ensure patient safety, the independence, composition, competence, and procedures of the DSMC will be considered among the review criteria.

AWARD CRITERIA

The anticipated date of award is September 30, 1994

Award criteria are:

o priority score
o availability of funds
o safety monitoring

An award is contingent on NIAMS approval of the DSMC and on verification that an FDA IND approval has been obtained for the antibiotic(s) to be tested.

INQUIRIES

Written and telephone inquiries concerning this RFA are encouraged.
The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues including application procedures, goals and scope of the RFA and guidelines for the DSMC to:

Dr. Susana A. S. Sztein
Rheumatic Diseases Branch,
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 405
Bethesda, MD 20892
Telephone: (301) 594-9953
FAX: (301) 594-9673

Direct inquiries regarding fiscal matters to:

Mrs. Diane M. Watson
Grants Management Officer
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 732A
Bethesda, MD 20892
Telephone: (301) 594-9965
FAX: (301) 594-9950

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846, Arthritis and Musculoskeletal and Skin Diseases Research. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

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